PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Trajectories of body mass index in adulthood and all-cause and cause-specific mortality in the Melbourne Collaborative Cohort Study
AUTHORS	Yang, Yi; Dugue, Pierre-Antoine; Lynch, Brigid; Hodge, Allison; Karahalios, Amalia; MacInnis, Robert; Milne, Roger; Giles, Graham; English, Dallas

VERSION 1 - REVIEW

REVIEWER	Raphael Simon Peter Institute of Epidemiology and Medical Biometry, Ulm University, Germany
REVIEW RETURNED	24-Apr-2019

GENERAL COMMENTS	This is an excellent manuscript with many strong points. I have only one comment which the authors might want to consider: Page 10, lines 226-7. “In never-smokers, all trajectories satisfied the proportional hazard assumption.” – Was this assessed via a statistical test? I am curious might this be the result of the lower numbers, while there, in reality, might still be an interaction with age in never-smokers? To clarify this, I propose to include in addition to the total HR also the age-specific estimates for non-smokers and TR6 in Table 2.

REVIEWER	Ming Ding Harvard T.H. Chan School of Public Health
REVIEW RETURNED	22-May-2019

GENERAL COMMENTS	In this study, Yi et al examined associations of trajectories of body mass index in adulthood and all-cause and cause-specific mortality among 29,881 participants. The authors found that a normal body weight across adulthood was associated with lower risks of total mortality and mortality due to CVD and obesity-related cancer. Main concerns 1. For data exclusion, the author excluded a lot of participants who were diagnosed with cancer before the last BMI assessment and were with less than three BMI data points. The author did not need

	to exclude participants with two BMI data, as a polynomial model can be fitted with two data points. Also, the author did not need to exclude participants diagnosed with cancer, but instead treat the BMI measured within two years of cancer diagnose as missing. Also, the BMI measured within two years of CVD, type 2 diabetes, and mortality should also be excluded. 2. As to trajectory analysis, how did the author select number of groups and the polynomial function of age? The author mentioned BIC and log Bayes factor at first, however, later mentioned model adequacy. Which criteria did the author use? Also, the author did not show whether the fitted model has adequacy in the result part. 3. What's the rationale of fitting models using last measured BMI as main exposure? Minor concerns 1. The abstract is not very informative. The author should describe exposure and outcome assessment, method of trajectory analysis, and the HR of total and cause-specific mortality. 2. The reference trajectory should be the higher-normal stable group, as the lower-normal stable group might have participants with diseases which can result in reverse causation. 3. Figure 3 can be a supplemental table.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Raphael Simon Peter

Institution and Country: Institute of Epidemiology and Medical Biometry, Ulm University, Germany

This is an excellent manuscript with many strong points. I have only one comment which the authors might want to consider:

Page 10, lines 226-7. "In never-smokers, all trajectories satisfied the proportional hazard assumption." – Was this assessed via a statistical test? I am curious might this be the result of the lower numbers, while there, in reality, might still be an interaction with age in never-smokers? To clarify this, I propose to include in addition to the total HR also the age-specific estimates for non-smokers and TR6 in Table 2.

Response: We thank the reviewer for the positive comment on our study. Yes, we assessed the proportional hazard assumptions in never-smokers via tests based on Schoenfeld residuals (page 8, line 169). We have added age-specific estimates for non-smokers to Table 2.

Reviewer: 2

Reviewer Name: Ming Ding

Institution and Country: Harvard T.H. Chan School of Public Health

In this study, Yi et al examined associations of trajectories of body mass index in adulthood and all-cause and cause-specific mortality among 29,881 participants. The authors found that a normal body weight across adulthood was associated with lower risks of total mortality and mortality due to CVD and obesity-related cancer.

Main concerns

1. For data exclusion, the author excluded a lot of participants who were diagnosed with cancer before the last BMI assessment and were with less than three BMI data points. The author did not need to exclude participants with two BMI data, as a polynomial model can be fitted with two data points. Also, the author did not need to exclude participants diagnosed with cancer, but instead treat the BMI measured within two years of cancer diagnose as missing. Also, the BMI measured within two years of CVD, type 2 diabetes, and mortality should also be excluded.

Response: We excluded participants with only two BMI data points because we wanted to assess quadratic patterns of BMI change over age (page 6, line 129). The probability of belonging to a quadratic trajectory is usually estimated through participants whose exposures were measured at three or more time points (1-3). As a quadratic trend of an exposure over age may increase, decrease, or remain stable up to a certain time point before changing in either magnitude or direction, it would be difficult to assign a participant's probability of belonging to a quadratic trajectory group based on only two measurements (4).

We excluded participants who were diagnosed with cancer before the last BMI assessment because sudden and unintentional weight loss is a common outcome of cancer that is associated with poor survival. We performed a sensitivity analysis excluding the first 2 years of follow-up (page 8, line 182) to assess the possible impact of pre-existing illnesses; results were unchanged (page 11, line 245).

2. As to trajectory analysis, how did the author select number of groups and the polynomial function of age? The author mentioned BIC and log Bayes factor at first, however, later mentioned model adequacy. Which criteria did the author use? Also, the author did not show whether the fitted model has adequacy in the result part.

Response: In the main text, we described the steps in selecting the number of groups and the polynomial function of age (page 6, line 139). We selected the number of groups and the polynomial function of age using the BIC and log Bayes factor. Once we had selected the model, we then tested its adequacy using the recommended criteria (5), as Nagin and Odgers (2010) stated that the choice of the best model specification cannot be reduced to the application of a single test statistic, and testing the adequacy of the selected model is an often-neglected step in the model selecting process in group-based trajectory modelling (6).

We have added further clarification in the Methods (page 7, line 145):

"The adequacy of the final model was evaluated using recommended diagnostic measures…"

in the Results (page 9, line 207):

"Model adequacy diagnostics are presented in Supplementary Table 1"

and the diagnostics have been added to Supplementary Table 1.

3. What's the rationale of fitting models using last measured BMI as main exposure?

Response: We compared models with BMI trajectories and models with last measured BMI.

The rationale was to assess whether the group-based trajectory approach yielded better prediction than the conventional approach in which BMI is measured at one time point only. To make the models comparable in terms of person-time with the trajectory analyses, we had to use the last measured BMI.

We have added the following clarification to the Methods (page 8, line 184):

“Finally, we compared the fit of the models with BMI trajectories and models with last BMI assessment, to assess whether trajectory models had better fit than models using the conventional approach based on one BMI assessment.”

Minor concerns

1. The abstract is not very informative. The author should describe exposure and outcome assessment, method of trajectory analysis, and the HR of total and cause-specific mortality.

Response: We have edited the abstract and added the main quantitative results.

2. The reference trajectory should be the higher-normal stable group, as the lower-normal stable group might have participants with diseases which can result in reverse causation.

Response: We believe that our choice of reference group is appropriate as it is within the normal BMI range recommended by international health guidelines (7). To address the potential issue of reverse causation, we excluded participants who were underweight at baseline (page 6, line 127).

3. Figure 3 can be a supplemental table.

Response: We have removed Figure 3 from the main text. The results from Figure 3 are presented in Supplementary Table 3.

Reference

1. Kelly SP, Graubard BI, Andreotti G, Younes N, Cleary SD, Cook MB. Prediagnostic Body Mass Index Trajectories in Relation to Prostate Cancer Incidence and Mortality in the PLCO Cancer Screening Trial. J Natl Cancer Inst. 2017;109(3). Epub 2016/10/22.

2. Niyonkuru C, Wagner AK, Ozawa H, Amin K, Goyal A, Fabio A. Group-based trajectory analysis applications for prognostic biomarker model development in severe TBI: a practical example. J Neurotrauma. 2013;30(11):938-45.

3. Kwon S, Janz KF, Letuchy EM, Burns TL, Levy SM. Developmental trajectories of physical activity, sports, and television viewing during childhood to young adulthood: Iowa Bone Development Study. JAMA pediatrics. 2015;169(7):666-72.

4. Andruff H, Carraro N, Thompson A, Gaudreau P, Louvet B. Latent class growth modelling: a tutorial. Tutorials in Quantitative Methods for Psychology. 2009;5(1):11-24.

5. Nagin D. Group-based modeling of development: Harvard University Press; 2005.

6. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. Annu Rev Clin Psychol. 2010;6:109-38.

7. WHO. Obesity: preventing and managing the global epidemic: World Health Organization; 2000.

VERSION 2 – REVIEW

REVIEWER	Raphael Simon Peter Institute of Epidemiology and Medical Biometry, Ulm University, Germany
REVIEW RETURNED	17-Jun-2019

GENERAL COMMENTS	All my comments have been addressed.

REVIEWER	Ming Ding Harvard T.H. Chan School of Public Health
REVIEW RETURNED	07-Jun-2019

GENERAL COMMENTS	My questions have been appropriately addressed.